REMARKS

The above newly entered paragraphs and the accompanying marked-up paragraph(s) of the specification overcome some informalities noted in the specification on file. The undersigned avers that the newly entered replacement paragraph(s) of the specification do not contain any new subject matter.

Claims 10-18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the reasons noted in the official action. The subject matter of the rejected claims is accordingly revised and rewritten as newly entered claims 19-31. The presently pending claims are now believed to particularly point out and distinctly claim the subject matter regarded as the invention, thereby overcoming all of the raised § 112, second paragraph, rejections.

Claims 10-18 are rejected, under 35 U.S.C. § 102(b), as being anticipated by Gierskcky et al. `412 and are also rejected, under 35 U.S.C. § 103(a), as being obvious over Gierskcky et al. `412 and Chang et al. The Applicant acknowledges and respectfully traverses the raised anticipatory and obviousness rejections in view of the following remarks.

The Examiner first refers to examples 1-4 (pp. 21-23) of Gierskcky et al. `412 as anticipating the previously pending claims of this application. However, the ".....methods of preparing solutions of 5-aminolevulinic acid esters" are described for preparation in the sense of "synthesis", and not administration, of ALA esters at concentrations lower than 0.5% by weight. It is, indeed, important to realize that these examples disclose the synthesis of ALA esters and not their administration for photodetection or phototherapeutic purposes. To persons skilled in the art of organic synthesis, it is obvious, taking into account the mass action law, that a reduction in the concentration of ALA in the preparation solution is more favorable for the synthesis of ALA ester (methylester in this particular example). However, newly entered independent claims 19 and 33 do not cover chemical synthesis. Instead, these claims cover preparation of a solution for therapeutic or diagnostic purposes which is administered to the patient to be treated.

In addition, it should be noted that, in particular with reference to Examples 1-4, excess solvents were removed by distillation to give a final concentration of 100% of dry powder. Moreover, under the conditions described in these examples, the solutions cannot be administered in vivo due to their high acidity and the methanol content. Therefore, they are not physiologically acceptable. This is in distinct contrast to newly entered claims 23 and 24 of the present application which correspond to appropriate solutions for application of the formulations disclosed in claims 19 and 20 as well as new claim 33.

With respect to the raised rejection of claims 10-18, under § 103(a) as being unpatentable over Gierskcky et al. '412 and Chang et al., the Applicant respectfully traverses the same in view of the following.

The principal difference between this prior art and the above mentioned application is that document Gierskcky et al. '412 particularly describes the preparation of ALA esters but does not relate to administration of these compounds at concentrations lower than 0.5% by weight to a patient while the publication of Chang et al. merely reports on the use of ALA only (and not on esters of ALA).

According to Gierskcky et al. '412, concentrations between 1% and 50% (more preferably 10% to 50%) are proposed for treatment purposes, while concentrations between 1% and 50% (more preferably 1% to 5%) are proposed for diagnostic purposes. However, in the case of several ALA esters and other derivatives of ALA, these concentration ranges will not lead to an optimal photosensitizer generation in the targeted tissues or cells. It has been previously shown by the inventors, and recently by other groups in vivo as well as in vitro (see for example in the enclosed references: Ref. 1 Fig. 4; Ref. 2 Table 1; Ref. 3 Figs. 3, 4, 5; and Ref. 4 Figs. 3, 4), that the ranges proposed in the Gierskcky et al. '412 reference--corresponding to 40 mM to 2000 mM for ALA hexylester--will not induce any photosensitizer synthesis in the tissues. In contrast, as demonstrated by the inventors in Refs. 1-3, this is only at concentrations lower than 20 mM, corresponding to 0.5% (w/w), that the photosensitizer biosynthesis can be observed (this was performed by detecting the photosensitizer's

fluorescence). In some cases, optimal photosensitizer synthesis can be observed at concentration as low as 0.2% by weight (see Ref. 2) or 0.005% by weight (also see Ref. 3). These observations are even more surprising when considering recent publications (Ref. 8), some of them being published by the inventors of the Gierskcky et al. '412 reference (Refs. 5, 6 7). All of them have shown protoporphyrin IX (PpIX) synthesis using ALA esters at *significantly higher* concentrations than those described in newly entered claims 19 and 33 of the present application. Furthermore, examples 7-15 of Gierskcky et al. '412 disclose the utilization of ALA esters at a general concentration of 20% by weight thereby indicating that the inventors of Gierskcky et al. '412 considered this concentration as being optimal. Therefore, it can be concluded that, according to the prior art, increasing and not decreasing the ALA derivatives concentrations was more obvious to a person skilled in the art in order to increase the buildup of photosensitizer. This is not the case with the present invention where only a concentration between 0.01 and 1% can be considered as being optimal, as presently recited in newly entered claims 19-35.

The Examiner also mentions that the use of iron chelators, such as EDTA, deferoxamine, CP94, etc., is described in earlier literature, e.g., Chang et al. and Gierskcky et al. '412, in order to reduce the amount of the applied drug and thereby the toxicity or the skin photosensitization, i.e., how to prepare a formulation generating at least similar activities photosensitizer production, while reducing the side effects described in the prior art.

It has to be mentioned that the Chang et al. publication relates to the use of ALA only (and does not relate to esters of ALA). One should, however, realize that from a chemical point of view, there is a significant structural difference between ALA and its esters. Additionally, the Applicants have previously shown that the addition of deferoxamine considerably increases the production of PpIX (as measured by a fluorescence intensity) when using ALA at 200 mM (Ref. 1). However, this situation changes drastically when using ALA hexylester at its optimal concentration of 4mM (i.e., 0.1%) under the same conditions (Ref. 1). It can be seen from the table presented on page 548 of the Ref. 1 that the addition of an iron chelating agent does not

significantly increase the biosynthesis of the photosensitizer, as it does using ALA at a 50 times higher concentration. This behavior is quite surprising, particularly for scientists familiar with the current state of this art.

The Applicants also draw the Examiner's attention to the fact that a Notice of Allowance was recently issued by the European Patent Office with respect to claims covering similar subject matter in the corresponding European patent application.

Concerning the rejection based under United States Patent Nos. 5,234,940, 5,955,490 and 5,856,566, the two former patents relate to the use of 5-aminolevulinic acid (ALA) in photochemotherapy and fluorescence photodetection, whereas the latter describes a sterilization (not the preparation or use of a drug) procedure for ALA. None of these three (3) additional patents is believed to be particularly relevant to the presently claimed invention.

Finally, it should be noted that the Applicant of Gierskcky et al. `412, being aware of the value and relevance of the present patent application in the field of photodynamic therapy and fluorescence photodetection, recently signed a license agreement with the Applicants of the above identified application.

If any further amendment to this application is believed necessary to advance prosecution and place this case in allowable form, the Examiner is courteously solicited to contact the undersigned representative of the Applicant to discuss the same.

In view of the above amendments and remarks, it is respectfully submitted that all of the raised rejection(s) should be withdrawn at this time. If the Examiner disagrees with the Applicant's view concerning the withdrawal of the outstanding rejection(s) or applicability of the Gierskcky et al. `412 and/or Chang et al. references, the Applicant respectfully requests the Examiner to indicate the specific passage or passages, or the drawing or drawings, which contain the necessary teaching, suggestion and/or disclosure required by case law. As such teaching, suggestion and/or disclosure is not present in the applied references, the raised rejections should be withdrawn at this time. Alternatively, if the Examiner is relying on his/her expertise in this field, the Applicant respectfully requests the Examiner to enter an affidavit

substantiating the Examiner's position so that suitable contradictory evidence can be entered in this case by the Applicant.

In view of the foregoing, it is respectfully submitted that the raised rejection(s) should be withdrawn and this application is now placed in a condition for allowance. Action to that end, in the form of an early Notice of Allowance, is courteously solicited by the Applicant at this time.

The Applicant respectfully requests that any outstanding objection(s) or requirement(s), as to the form of this application, be held in abeyance until allowable subject matter is indicated for this case.

In the event that there are any fee deficiencies or additional fees are payable, please charge the same or credit any overpayment to our Deposit Account (Account No. 04-0213).

Respectfully submitted,

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CERTIFICATE OF TRANSMISSION

I hereby certify that this correspondence is being transmitted via facsimile to the United States Patent and Trademark Office on: June 27, 2002.

Michael J. Bujold
Type name of person signing certificate

09/673,871

VERSION WITH MARKINGS TO SHOW CHANGES MADE

PAGE 3, 1st PARAGRAPH

This goal is achieved using a 5-aminolevulinic acid ester (E-ALA) such as that defined in the preamble, characterized in that the concentration C of E-ALA in the solution is less than 1% and ranges ~~form~~ **from** 0.01% to 0.5% (0.01% ≤C≤ 0.5%).

PAGE 4, 3rd FULL PARAGRAPH

The solution can be completed by the addition of a complementary substance to prevent the PpIX ~~into~~ from transforming into a heme by iron complexing in the living cells. This complementary substance may be an EDTA (tetra acetate diaminoethyl), deferroxamine or desferal.